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SALO GRONOWITZ


# Substituent effects in thiophenes with particular regard to 3-substituted compounds

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# Substituent effects in thiophenes with particular regard to 3-substituted compounds

*INAUGURAL DISSERTATION*

BY

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BY DUE PERMISSION OF THE FACULTY OF
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# Substituent effects in thiophenes with particular regard to 3-substituted compounds

By Salo Gronowitz

With 3 figures in the text

## Introduction

Through the discovery of the commercial thiophene synthesis from butane and sulphur in 1946 (19) new interest in thiophene research grew rapidly, but for 30 years until 1941 it had been carried out mainly by Steinkopf and coworkers (20).

New reactions, more or less specific for thiophene, such as the chloromethylation (21), the formylation with N,N-substituted formamides (22), the metalation with *n*-butyllithium (23), the acylation (24) and alkylation (25) catalyzed by strong oxy-acids, to mention some, were discovered.

The main interest of thiophene research, however, has been on the pharmacological plane. Blicke (26), Buu-Hoi (27) and Cymerman-Craig (28), among others, have prepared thiophene analogs of known biologically active benzene derivatives. Their work has almost exclusively been devoted to the easily prepared 2-substituted derivatives.

In recent years thiophene compounds have become of great preparative importance for the synthesis of aliphatic compounds through Raney-nickel desulphurization. Hansen, Buu-Hoi *et al.* and especially Goldfarb and coworkers have shown that aliphatic carboxylic acids (29), amino acids (30), amines (31), alcohols (32), amino-alcohols (33) and ethers (34), can be prepared from thiophene compounds. Fredga (35) has demonstrated the usefulness of Raney-nickel desulphurization of thiophenes for steric correlation of benzene derivatives with aliphatic compounds.

It was soon realized that thiophene showed a very versatile reaction pattern and that superficial statements, which can be found in almost every text-book of organic chemistry, like "thiophene is very similar to benzene, perhaps somewhat more reactive" have only hindered the development of our knowledge of thiophene chemistry. It is ironic that this overemphasis of the similarity between benzene and thiophene stems directly from the discoverer of thiophene, the great Victor Meyer (36). This is understandable, considering the well-known circumstances of its discovery, but it is unfortunate that quantum chemists have a tendency to overestimate the similarity between thiophene and benzene (37). However, in more recent quantum-mechanical calculations (38, 39) the great differences between benzene and thiophene are also stressed. According to Hartough (40) thiophene and benzene ought to be compared "about as closely as a zoologist would compare the tortoise and the boa constrictor, they are in the same class but of widely separated species".

In order to study the aromatic character of thiophene, Fredga and coworkers (41, 42) have investigated optically active 2-substituted thiophenes. As a link in these investigations and in order to elucidate the differences between 2- and 3-substituted thiophenes and the corresponding benzenes, the present author has studied IR- (10), UV- (11) and NMR-spectra (12) of 3-substituted thiophenes, the optical activity of such compounds (13, 14, 16, 17) as well as the directing effect of substituents in position 3 on substitution reactions (6, 7, 9).

## Preparation of 3-substituted thiophenes

The first problem connected with this investigation has been to work out methods for the preparation of 3-substituted thiophenes. Since the fundamental work of Victor Meyer it has been known that most substitution occurs almost exclusively in the 2-position. Among the few reactions which are known to lead to predominant 3-substitution may be mentioned the phenylation of thiophene through decomposition of nitroso acetanilide in thiophene (43) and the gas-phase bromination of thiophene (44), discovered some years ago, which gives 3-bromothiophene in low yield. None of these methods are of preparative value. More important however is the sulphuric acid catalyzed alkylation of thiophenes which gives 2- and 3-substitution in about equal amounts (45).

Indirect and tedious methods have therefore been used and only a few compounds have been prepared. The slight knowledge we have had of 3-substituted thiophenes is perhaps best illustrated by the fact that in Hartough's monograph on thiophene, only 8 pages (46) of over 500 are devoted to the 3-substituted compounds.

Since 1948 Campaigne *et al.* (47) have prepared 3-substituted thiophenes from 3-methylthiophene through side-chain bromination with N-bromosuccinimide. The main interest of Campaigne has been to prepare pharmacologically active 3-substituted compounds (48) and to compare their activity with the 2-isomers and the benzene analogs.

The pro and contra of this method has been discussed by the present author (1), and a modification which gives more reproducible results has been introduced. 2-Bromo-3-methylthiophene, which was formed as a by-product in the bromination, could also be utilized for the preparation of 3-substituted thiophenes (2). After completed reaction, the halogen atom was removed through reduction with sodium amalgam. Through these methods, 3-thenylsuccinic acid (1, 2) has been prepared for a study of its optical antipodes.

Because of the difficult availability and high price of 3-methylthiophene, the present author has also studied the chloromethylation of 2,5-dihalogensubstituted thiophenes (2). 3-Chlormethyl-2,5-dichlorothiophene was obtained through chloromethylation of 2,5-dichlorothiophene with chloromethyl ether. Via this compound, 3-thenylsuccinic acid was obtained after removal of the chlorine with sodium amalgam.

Most of the 3-substituted thiophenes were prepared from 3-bromothiophene. This compound was synthesized by a method first described by Steinkopf *et al.* (49) who obtained such a low yield that he abandoned this method and worked out another much more tedious route to 3-bromothiophene (50). The present author (3), however, obtained good yield with the first mentioned method which consists in grignardation of both $\alpha$-bromines of 2,3,5-tribromothiophene in the presence of large amounts of ethyl bromide (entrainment method). Upon hydrolysis of the Grignard compounds

3-bromothiophene was obtained in good yield. As this preparation is the foundation for the subsequent synthesis of 3-substituted thiophenes, the mechanism of the entrainment Grignard reaction has been studied to a certain extent (4).

It has recently been proposed (51) that it should be more suitable and better to carry out the dehalogenation with *n*-butyllithium. It seems however to the present author very improbable that this two-step method which demands the prior preparation of *n*-butyllithium, the preparation and handling of which in large amounts is rather elaborate, can offer any advantage over the one-step entrainment method. The present author (2, 5) however has earlier pointed out that dehalogenation with *n*-butyllithium is of importance in such cases when the entrainment method cannot be used, as in the preparation of 4-bromo-2-thiophenecarboxylic acid from 4,5-dibromo-2-thiophenecarboxylic acid. Recently Imoto *et al.* (52) have described a modification of Steinkopf's second method. They obtained 3-bromothiophene in one step from 4,5-dibromo-2-thiophenecarboxylic acid through simultaneous decarboxylation and debromination with copper powder in quinoline.

From 3-bromothiophene it was possible to obtain 3-methoxythiophene (6) through the cupric oxide catalyzed reaction with sodium methylate in methanol. Most of the 3-substituted thiophenes were however prepared via 3-thienyllithium, which was obtained through halogen-metal interconversion between 3-bromothiophene and *n*-butyllithium (7). Because of the presence of the reactive α-hydrogens, 3-thienyllithium is only stable at low temperature, so the reactions were carried out at $-70^{\circ}$C. If the halogen-metal interconversion is carried out at higher temperature, metalation of 3-bromothiophene in the 2-position is obtained. It has been shown by the present author that this is mainly because the initially formed 3-thienyllithium metalates 3-bromothiophene faster than the latter undergoes halogen-metal interconversion with *n*-butyllithium. Similar results have afterwards been obtained by Lawesson in the reaction of 3,4-dibromothiophene (53) and 2,4-dibromothiophene (54) with *n*-butyllithium.

Through the reaction of 3-thienyllithium with carbon dioxide, a convenient method for the preparation of 3-thiophenecarboxylic acid (7) was obtained. 3-Thiophenecarboxaldehyde and 2-(3-thienyl)-ethanol were obtained through the reaction of 3-thienyllithium with N,N-dimethylformamide and ethylene oxide respectively (2). 3-Thienylsubstituted secondary alcohols were obtained through the reaction of 3-thienyllithium and aromatic or aliphatic aldehydes (8). These alcohols could easily be oxidized to the corresponding ketones with chromic oxide in acetic acid. Through the reaction of 3-thienyllithium with cyclohexanone and aromatization of the obtained cyclohexenylthiophene, 3-phenylthiophene was prepared in good yield (55). Dimethyl disulphide reacted with 3-thienyllithium to give methyl 3-thienyl sulphide in good yield (9). This compound was easily oxidized with hydrogen peroxide to the corresponding sulphone (9). 3-Thienylsulphinic acid was obtained in the reaction between 3-thienyllithium and sulphur dioxide (9). 3-Thiopheneboronic acid was obtained by Lawesson (56) through the reaction of 3-thienyllithium and *n*-butyl borate.

As 3-thienyllithium is a very reactive and rather unselective reagent, the present author has investigated the possibility of transferring 3-thienyllithium into more selective metal-organic compounds through the reaction with zinc chloride, cadmium chloride and magnesium bromide (8). Through reaction with magnesium bromide, the Grignard reagent free from entrainment Grignard reagent was obtained and through reaction with acetic anhydride at low temperature, 3-acetothienone was

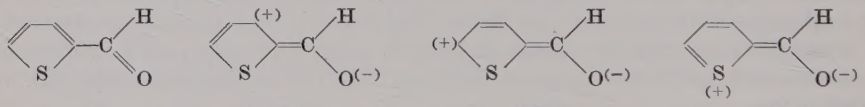
obtained in high yield (8). 3-Thienyllithium reacted slowly with cadmium chloride, but could rapidly be transferred to the zinc organic compound with zinc chloride. In the reaction with acetyl chloride the present author (8, 57) discovered a new type of rearrangement reaction which led to a mixture of 2- and 3-acetothienone. This rearrangement is not specific for the thiophene series but has afterwards independently been found in the benzene series. Thus Klemm, Mann and Lind (58) obtained in the reaction between *meta* methoxybenzenemagnesium bromide, cadmium chloride and *meta* methoxybenzoyl chloride a mixture of the *meta* and *para* isomers.

A new method for the preparation of 3-substituted thiophenes has recently been introduced by Wynberg *et al.* (59). They reacted 3-ketotetrahydrothiophene with Grignard reagents or organolithium compounds. The tertiary alcohols thus obtained were dehydrated and the unsaturated compounds aromatized with chloranil or sulphur. This method however does not offer any advantage over the 3-thienyllithium method for instance for the preparation of 3-phenylthiophene (55).

Through a combination of both methods it should however be possible to prepare otherwise difficultly available compounds. Thus 3,3-dithienyl ought to be easily prepared through the reaction of 3-thienyllithium with 3-ketotetrahydrothiophene.

## Effects of substituents in position 2 in thiophene

If the following resonance structures are assumed to contribute to the structure of 2-substituted thiophenes containing a $-I-M$ substituent,[1]



I II III IV

it is apparent that the substituent effect is parallel to that in the corresponding benzenes. Structure IV can according to Melander (39) be assumed to have a low mixing coefficient as it contains a C=S double bond. Dipole moment measurements on 2-nitrothiophene (60, 61) and 2-acetothienone (62) are in accordance with this structure. The 3-, 4- and 5-positions can thus with a certain right be compared with the *ortho*, *meta* and *para* positions in substituted benzenes. Until Rinkes' (63) investigations in the earlier 1930's on the nitration of 2-thiophenecarboxylic acid it was also generally believed that electrophilic substitution occurred in the 4-(*meta*-)position. Rinkes however showed that the main product in his nitration experiment was 5-nitro-2-thiophenecarboxylic acid and that thus the place of substitution was determined in competition between the *meta*-directing effect of the substituent and the 5-directing effect of the heterocyclic sulphur. Through different investigations it was soon clear that the proportion of 4- and 5-isomer formed was related to the *meta*-directing strength of the substituent. Steinkopf and Höpner (64) thus found that in the nitration of 2-nitrothiophene, 80 % 2,4-dinitrothiophene, and 20 % 2,5-dinitrothiophene was formed and that in the nitration of 2-thiophene sulphonyl chloride, 75 % of the 4-isomer and 25 % of the 5-isomer was formed. Recently Blatt *et al.* (65) have reinvestigated the nitration of 2-nitrothiophene and obtained about 85 % 2,4-

[1] The terminology of Ingold will be used throughout this paper.

and 15 % 2,5-dinitrothiophene. Blatt points this out especially since some confusion has arisen out of misinterpretation (66) of Steinkopf's results. Recently Tirouflet and Fournari (67) have published some elegant work on the nitration of 2-substituted thiophenes containing a −I−M substituent. The analyses were carried out through polarography. Their results are given in the following table.

| | CHO | $COCH_3$ | CN | COOH | $CH(OCOCH_3)_2$ |
|---|---|---|---|---|---|
| % 4-isomer | 75 | 52 | 43 | 31 | 14 |

It is thus apparent that the proportion of 4-isomer rises with increasing *meta*-directing effect of the substituents in the corresponding benzenes, as measured in the ratio *meta* to *ortho-para* or proportion *meta*, when a $-CH_2-$ is included between the phenyl ring and the substituent (68). The effect of a −I−M substituent in the 2-position of thiophene has been discussed at some length as there have lately been tendencies in the literature (56, 69) to overestimate the α-directing effect of the sulphur. The similarity between the 2,5-positions in thiophene and the *para* positions in benzene is also evident from the results of Imoto *et al.* (70). In a study on the esterification and hydrolysis of 5-substituted 2-thiophenecarboxylic acids, they found that Hammett's law was applicable to these compounds and obtained ϱ-values which were approximately equal for benzenes and thiophenes.

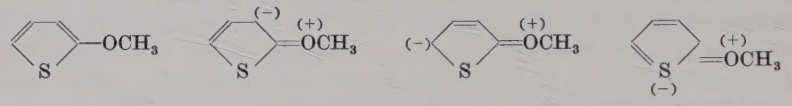
The substituent effect of 2-substituted thiophenes differs noticeably however from the corresponding benzene compounds in certain aspects. Although the classification of substituents has to a large extent been founded on the nitration reaction (71) it is generally believed that the same directing rules also apply to other electrophilic substitutions, at least when the *meta*/*para* ratio is considered. The present author (5) has pointed out that this seemed not to be the case in the thiophene series. In the bromination of 2-thiophenecarboxaldehyde 5-bromo-2-thiophenecarboxaldehyde was obtained almost exclusively (5); in the corresponding nitration, 75 % of the 4-isomer is obtained (67). The same results have recently been obtained by Buu-Hoi and Lavit (69) apparently independently. It seems improbable that the primary step in the bromination is an addition, as Lawesson (51) did not obtain any addition products in his investigation on the bromination of thiophene. It is of course always possible that the α-bromination occurs via a cyclic mechanism in which the sulphur atom is involved. It should be remembered however that if the *meta* directing group in the 2-position is combined with a +I substituent in position 3, bromination occurs predominantly in the 4-position. Thus according to Steinkopf and Nitschke (72), 4-brom-3-methyl-2-thiophenecarboxylic acid methyl ester is obtained on bromination of 3-methyl 2-thiophenecarboxylic acid methyl ester. The most plausible explanation appears to the present author to be that in the nitration reaction, it is not the effect of for instance the carbonyl group itself which is studied, but of its conjugate acid obtained through the addition of a proton to the carbonyl oxygen of the stronger acidic medium. This neutralizes the negative charge on the oxygen and makes the substituent more effectively *meta*-directing by deactivating the 3- and 5-positions more strongly than the −C=O group itself, the effect of which is measured in the bromination reaction.

Another peculiarity of a −I−M substituent in the 2-position of thiophene as compared with the corresponding benzene derivative is the apparent strong deactivation of the 3-position in thiophene. It is well known from benzene chemistry that the main by-product in electrophilic substitution is the *ortho* isomer (73). In the

corresponding thiophene compound however it is impossible to introduce a substituent in position 3. Thus 2-thiophenecarboxylic acid can only be brominated to the 4,5-dibromo acid (74). Under more vigorous conditions the substituent is eliminated.

When substituents with weak directing effect such as halogens or alkyl groups are introduced in position 2, the strong effect of the sulphur atom dominates, and substitution appears to occur almost exclusively in position 5. The only accurate investigation which has been made is the chlorination of 2-chlorothiophene (75) in which only very minute amounts of the 2,3-isomer were obtained.

If, however, a powerful *ortho-para* directing substituent is introduced in the 2-position, it activates position 3 strongly enough to compete with position 5. Thus Sicé (76) obtained 24 % of 2-methoxy-3-nitrothiophene, and 36 % of 2-methoxy-5-nitrothiophene on nitration of 2-methoxythiophene. This is in accordance with the following structures assumed to contribute to the structure of 2-methoxythiophene (6), from which it can be seen that position 3 and 5 are activated to electrophilic substitution. The 5 position is also activated by the sulphur.



V VI VII VIII

Structure VIII is assumed to be of very low weight, as it has a decet around the sulphur as well as a C=S double bond.

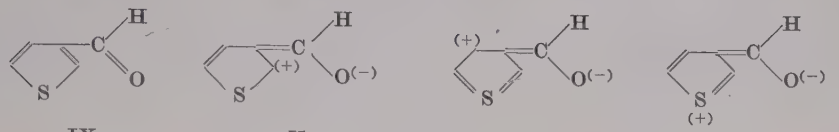
## Effects of substituents in position 3 in thiophene

Very little is known about the directing effect of substituents in position 3. 3-Methylthiophene has been investigated to a certain extent. Upon acylation, 20 % of the 5-isomer was obtained (24). In other electrophilic substitutions only minute amounts of this isomer were isolated, and the 2-isomer was obtained almost exclusively (77). Campaigne and Bourgeois (78) have recently investigated the chlorination, bromination and nitration of 3-thiophenecarboxylic acid. They found that the first substituent entered the 5-position and that a second substituent could be introduced into the 2-position, except in nitration where only monosubstitution could be achieved. Campaigne and Monroe (79) have also investigated some substitution reactions of 3-actylaminothiophene and found that monosubstitution occurred in position 2 and disubstitution in positions 2 and 5.

Already Steinkopf (80) observed the ease with which electrophilic substitution occurred in position 4 in thiophenes containing a $-I-M$ substituent in position 3 if the reactive $\alpha$-positions are blocked with methyl groups or halogens. They managed easily to dinitrate and disulphonate 2,5-dimethylthiophene (49, 81) and 2,5-dibromothiophene (49). Steinkopf (82) also found that three acetoxymercury groups could be introduced in 3-nitrothiophene compared with only two in 2-nitrothiophene under the same conditions. They (49) thus concluded that the 3,4-positions in thiophene could not be compared with either *ortho* or *para* positions in benzene, but reminded one of the *peri* positions in naphthalene if any comparison must be made. The present author and Rosenberg (10) also found that 2,4,5-tribromo-3-thiophenecarboxylic acid could be easily obtained through extensive bromination of 3-thiophenecarboxylic

acid. The explanation of Hartough that all these experimental facts can be explained through an addition mechanism seems somewhat unlikely (83).

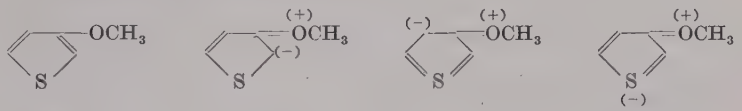
The present author and Rosenberg (10) suggested, after a discussion of the following resonance structures,



IX X XI XII

that a structure like XI should have very low weight as it has a decet around the sulphur and that thus a $-I-M$ substituent should not deactivate position 4 in electrophilic substitution in accordance with the experimental results cited above. This is also in accordance with molecular orbital calculations by Melander (39) who also pointed out that structure XII should also have low weight, as it contains a C—S double bond.

The present author (6) has also carried through the corresponding discussions for a $-I+M$ substituent in position 3, examplified in 3-methoxythiophene. It was suggested that of the following resonance structures, only XIII and XIV are of importance. As a consequence, a $-I+M$ substituent should not conjugatively activate position 4 against electrophilic substitution. Instead, the associated $-I$ effect should deactivate this position.



XIII XIV XV XVI

There are certain experimental results which are in accordance with the suggested structure. As mentioned earlier, a methoxy group in position 2 activates position 3 enough in electrophilic substitution so that this position can compete with position 5, which is also activated by the sulphur (76) towards the reagent. When however an acetylamino group is placed in position 3, monosubstitution is apparently obtained only in position 2 and disubstitution in 2 and 5 (79) although it is known from competitive experiments in the benzene series (84) that the $-NHCOCH_3$ group is a stronger activating *ortho-para* directing substituent than the $-OCH_3$ group.

If we look at the electronic properties of the thienyl nucleus, it seems probable from the suggested structures that the 2-thienyl group is a stronger $+M$ as well as $-M$ substituent than the 3-thienyl group. It should perhaps be pointed out that these conclusions are drawn under the assumption that the quotients of the mixing coefficients for I and II are of the same magnitude as IX and X and in the same manner for V and VI, XIII and XIV, which seems reasonable.

As to the inductive effect, the dissociation constants of 2- and 3-thiophenecarboxylic acid indicate that the electron-attracting inductive effect of the 2-thienyl group is much stronger than that of the 3-thienyl group. 2-Thiophenecarboxylic acid is stronger than the 3-isomer (85), although the conjugation effect should tend to diminish the acid strength more in the 2- than the 3-isomer. (Because of an unfortunate inadvertance it was suggested (10) that the greater acid strength of 2-thiophene-

carboxylic acid was related only to the conjugative effect.) A very extensive discussion of the influence of the inductive and conjugative effects on the acid strength of benzoic acid, and of the possibility to estimate the magnitude of these two opposite effects has been given by Brown *et al.* (86). According to the investigation of Wepster (87), the −I and +M effect of the phenyl group are of the same order and as a consequence, benzoic acid has about the same acid strength as acetic acid. To judge from the acid strength, the −I effect of the 2-thienyl group appears to be appreciably greater than its +M effect, for the 3-thienyl group they appear to be of the same order.

## IR-spectra

As a consequence of the suggested structures for 2- and 3-thienylsubstituted carbonyl compounds as the aldehydes and the acids, the C=O bond in 2-substituted compounds ought to have larger single-bond character than in the 3-isomers. A possibility to study the differences in conjugation between these compounds is thus offered by the C=O stretching band in the IR-spectrum (88), as it is generally accepted that conjugation results in a shift of this band towards lower frequency (89, 90 91) and its frequency should be proportional to the force constant, which in turn should be related to the character of the C=O bond. In Table 1, a collection of the C=O frequency for different carbonyl containing 2- and 3-substituted thiophenes is given.

*Table 1.* C=O frequency of monosubstituted thiophenes.

| Substituent | Position 2 C=O frequency $cm^{-1}$ | Position 3 C=O frequency $cm^{-1}$ |
|---|---|---|
| CHO | 1673 | 1691 |
| $COCH_3$ | 1658 | 1674 |
| $COCHO \cdot H_2O$ | 1673 | 1689 |
| COOH | 1679 | 1690 |
| $COC_6H_5$ | 1636 | 1652 |

As can be seen the results are in accordance with stronger conjugation in the 2-isomers. Soloway and Friess (92) have pointed out that there is a connection between the C=O frequency of substituted acetophenones and the carbonyl reactivity as expressed in Hammett's $\sigma$-values. They obtained no linear relationship, as some C=O frequencies were measured in the solid state. Later Jolien *et al.* (93) have investigated the C=O frequency of substituted benzophenones in dilute solution and found a linear relationship between C=O frequency, Hammett's $\sigma$-values and the half-wave potential in polarographic reduction.

It is therefore of some interest to compare the frequency in the thiophenealdehydes with some substituted benzaldehydes (88) given in the table below.

If the comparison between side-chain reactivity and C=O frequency could be extended to the thiophene series, 2-thiophenealdehyde should undergo carbonyl reactions with a rate comparable with a benzaldehyde heavily substituted with electron-donating substituents such as vanillin and 3-thiophenecarboxaldehyde ought to be comparable with anisic aldehyde. However, few quantitative measurements of such reactions have been carried out. A quantitative study on the rate of alkaline

*Table 2.* C=O frequency of some aromatic aldehydes.

| Aldehyde | C=O frequency, $cm^{-1}$ |
|---|---|
| p-Nitrobenzaldehyde | 1721 |
| Benzaldehyde | 1704 |
| β-Naphthaldehyde | 1702 |
| α-Naphthaldehyde | 1700 |
| 3-Thiophenealdehyde | 1691 |
| m-Hydroxybenzaldehyde | 1691 |
| p-Hydroxybenzaldehyde | 1690 |
| Vanillin | 1676 |
| 2-Thiophenealdehyde | 1673 |

hydrolysis of the isomeric ethyl thiophenecarboxylates has been carried out by Price *et al.* (85, 94). According to the latest of these investigations it seems that the rates are very similar to that of ethyl benzoate and the order of influence on the rate is 2-thienyl > phenyl > 3-thienyl. This might indicate that a general connection between C=O frequency and reactivity for different series of compounds cannot be expected. This is in accordance with the conclusion of Price (85) that Hammett's σ-values cannot be obtained for thiophene derivatives with benzene as a base. Such σ-values can however be obtained with thiophene as a base which also has been shown by Imoto *et al.* (70) and by Tirouflet and Chané (95).

## UV-spectra

Another possibility to study the conjugation in thiophene compounds is offered by an investigation of their UV-spectra.

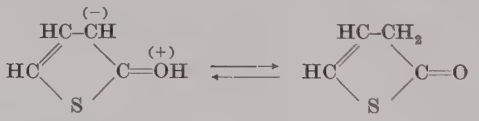
It is well known that increasing conjugation stabilizes the excited state more than the ground state and causes the bathochromic shift. The explanation for this in valence bond terminology is that dipolar structures make larger contributions to the excited state than to the ground state (96). Phenomena involving the excited state should be more affected by differences in the electron-attracting or electron-repelling properties of the substituent than the ground state. There is evidence however that in most cases these effects are similar in the ground state. Thus Doub and Vandenbelt (97) found that there was a large parallelity between the bathochromic shift in −I−M substituted benzenes and the −M effect of these substituents. Large parallelity has also been obtained between chemical data for alkyl benzenes and the shifts in their UV-spectra, which led Matsen *et al.* (98) to the conclusion that the excited state produced in aromatic compounds by the absorption of light must resemble in a number of ways the transition state for the substitution reaction.

An investigation of 20 monosubstituted thiophenes (11) has made it possible to interpret the spectra of these compounds to a certain extent and to discuss the difference between 2- and 3-substituted compounds. Larger bathochromic shifts were obtained for 2-substituted thiophenes containing −I−M substituents than for the corresponding 3-isomer, giving additional evidence for the stronger conjugation in the 2-substituted derivatives. Indication for the stronger conjugation in 2-substituted thiophenes containing +M substituents than in the 3-isomers, were also obtained, although in this case the results were not so clear cut.

## NMR-spectra

The best possibility for studying the electron distribution at the aromatic hydrogens in the ground state is offered by high resolution nuclear magnetic resonance spectroscopy, since according to Ramsay (99) and Gutowsky *et al.* (100) the chemical shifts observed in proton magnetic resonance due to diamagnetic shielding of the nucleus are connected with differences in the electron distribution around chemical non-equivalent protons. Corio and Dailey (101) have studied monosubstituted benzenes and discussed the connections between the electronic properties of the substituents and the chemical shifts in the NMR-spectra. The situation is, however, more complex with benzene compounds than with the thiophene analogs, since in the former there are five protons, the spin-spin coupling of which complicates the spectra and makes assignment of the protons relatively difficult. In monosubstituted thiophenes on the other hand there are only three aromatic hydrogens and the spin-spin coupling constants can be used for the identification of the different protons (12) in those cases when resolved spectra were obtained. NMR-spectra give the possibility to estimate more quantitatively the difference between the $\alpha$- and $\beta$-hydrogens in thiophene, and facilitate in this way the discussion of the shifts caused through the substituents.

The spectrum of 3-methoxythiophene (12) illustrates the enormous difference between hydrogen 2 and hydrogen 4 giving strong evidence for the correctness of the suggested structure of this compound. The NMR data demonstrate also the permanent nature of the conjugative effect of the metoxyl group. The larger shift for the 3- and 5-hydrogens in 2-methoxythiophene and for the 2 hydrogen in 3-methoxythiophene as compared to the shifts in anisole, make it reasonable that the dipolar structures like VI and VII in 2-methoxythiophene and XIV in 3-methoxythiophene should have larger coefficients than the corresponding resonance structures for anisole. It seems plausible to the present author that there is a connection between the importance of such resonance structures for thiophenes with +M substituents




and the tautomeric nature of the very instable thienols (102, 103). Although no quantitative determination of the equilibrium position of the tautomeric system has been made in solution, the experimental results indicate that the keto form dominates for the 2-isomer. Ford and Mackay (103) state that 3-hydroxythiophene, though also tautomeric, appears to be more phenolic than the 2-isomer.

The NMR-spectra of the isomeric methyl thienyl sulphides indicate that the tautomeric effect of the $-SCH_3$ group in aromatic substitution is largely electromeric in nature.

The NMR-spectra are also in accordance with the interpretation that a −I−M substituent conjugates with the thienyl groups to a greater extent than the phenyl group, although the differences appear to be smaller than when +M substituents are considered. The special effect of the substituent in position 3 on position 4 is also evident (cf. tables in (12)). The connection between the electron-densities obtained from NMR-spectra of −I−M substituted compounds and the isomer ratio obtained in electrophilic substitution has been discussed.

## Optical activity

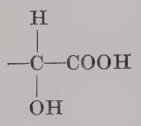
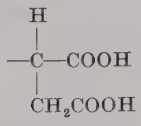
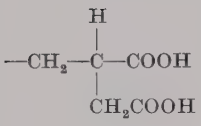
Kuhn (104) has recently pointed out that through the large amount of work on the connection between the direction of rotation in optical active compounds and configuration, which arose through the discovery of the Walden inversion, a certain knowledge of the connection between chemical constitution and optical rotation has been obtained, and that through this knowledge optical rotation data should give valuable information about the structure of organic compounds. This was realized 10 years ago by Fredga (41) who started an investigation on optically active thiophene compounds in order to throw some light on the aromatic nature of these compounds. Fredga and his collaborators (105) especially Pettersson (42) have investigated 2-substituted thiophenes, and by extending it to the 3-substituted compounds it was hoped to obtain additional information about the differences and similarities between the phenyl and the 2- and the 3-thienyl nuclei.

The present author has studied 3-thenylsuccinic acid (13) and 3-thienylsuccinic acid (14), the corresponding 2-isomers have been investigated by Fredga and Palm (41) and by Pettersson (106) and the benzene analogs by Fredga (107) and by Pettersson (108). The present author has also investigated both thiophene analogs of mandelic acid (15, 16, 17), as these acids are especially interesting since optically active mandelic acid is a well investigated compound, whose rotation dispersion has been discussed (109).

The first step in the synthesis of 3-thenylsuccinic acid (1) was side-chain bromination of 3-methylthiophene. The 3-thenyl bromide obtained was reacted with triethyl sodium ethane 1,1,2-tricarboxylate and the triester obtained was hydrolyzed and decarboxylated to 3-thenylsuccinic acid. The (−)-antipode was obtained through the strychnine salt and the (+)-antipode through the (+)-α-phenylethylamine salt (13). 3-Thienylsuccinic acid was obtained by condensing 3-thiophenecarboxaldehyde with ethyl malonate adding KCN over the double bond and hydrolyzing and decarboxylating the obtained cyano ester (2). The (+)-antipode was obtained through the cinchonidine salt and the (−)-form through the (−)-phenylethylamine salt (14). The isomeric thienylglycolic acids were obtained through oxidation of the methyl ketones with $SeO_2$ to the glyoxals and rearrangement of the latter in alkali (15). The (+)-form of the 2-isomer was obtained through the (−)-α-phenylethylamine salt and the (−)-form through the cinchonidine salt (16). The (+)-form of the 3-isomer was obtained through the strychnine salt and the (−)-form through the (+)-α-phenylethylamine salt (17).

The absolute configurations of these acids were determined by the Fredga quasi-racemate method (110) and also through the desulphurization method introduced by Fredga (35). Through this method a new determination of the configuration of mandelic acid has been carried out via 2-thienylglycolic acid (16). The quasi-racemate method has recently been extensively discussed (42, 111). It should therefore only be pointed out that X-ray powder photographs have been used extensively in order to identify the quasi-racemate and they are very useful to correlate thiophene and benzene compounds as the 2- and 3-thienyl compounds often are isomorphous with the benzenes (13, 14). This stresses the view that the large similarity between the thiophenes and benzenes is related to such physical properties as shape, size and molecular weight, which are reflected in the melting and boiling points, and, that these similarities often unfortunately have been generalized to be true for chemical reac-

*Table 3.* Optical activity of some thienyl and phenyl substituted compounds.

| Substituent | $[M]_D^{25}$ in ethanol | | |
|---|---|---|---|
| | phenyl | 2-thienyl | 3-thienyl |
|  | +228° (16) | +139° (16) | +162° (17) |
|  | +280° (108) | +207° (106) | +205° (14) |
|  | +43.5° (107) | +16.3° (41) | +32.1° (13) |

tivity. The usefulness of the IR-method introduced by Rosenberg and Schotte (112) for the identification of quasi-racemates has also been demonstrated (13, 14, 16, 17).

The rotations in ethanol for the resolved 3-substituted thiophenes and the corresponding 2-isomers and phenyl analogs are given in Table 3.

It can be seen that for the glycolic acids and the acids of the benzylsuccinic acid type the rotation for the 3-isomers lies between those of the phenyl compound and the 2-thienyl derivatives. The rotations of the isomeric thienylsuccinic acids on the other hand show a remarkable similarity in all solvents investigated (14). All these compounds show normal rotation dispersion in the visible which can be represented by the Drude formula. As an example the rotation dispersions for mandelic acid and the thienylgylcolic acids are given in Table 4.

*Table 4.* Rotation dispersions in water.

| Compound | $[M]^{25}$ in $H_2O$ | | | |
|---|---|---|---|---|
| | 6438 | 5893 | 5461 | 5086 |
| Mandelic acid | +189° | +229° | +277° | +337° |
| 3-Thienylglycolic acid | +159° | +192° | +232° | +278° |
| 2-Thienylglycolic acid | +125° | +154° | +181° | +215° |

The experimental material is of course still too small to draw positive conclusions with certainty. However some attempts will be made to discuss the results in terms of the Kuhn-Freudenberg theory on the connection between optical activity and chemical constitution (113).

According to this theory the contribution to the optical rotation from the 250 mμ band in certain benzenes determines the magnitude of the rotation in the visible region, partly depending upon the fact that this band is near to the visible region, and partly, and what is more important, the vicinal action of the other substituents makes this band highly anisotropic. In order for this benzene band to become anisotropic and the phenyl group thus a dominating (massgebender) substituent it is necessary that the phenyl group is directly attached to the asymmetric center. This is however not enough. In certain cases such as in methyl phenyl carbinol (109) the 250 mμ band does not become anisotropic and makes no contribution to the rotation in the visible. Rotation dispersion investigations in this band of mandelic acid and hydratropic acid have shown (109) that in these compounds the 250 mμ band is highly anisotropic. The similar rotation values for phenylsuccinic acid and mandelic acid and their similar dispersion in the visible indicate that this also is the case in phenylsuccinic acid. If in such a dominating substituent small changes are made (e.g. substituents are introduced in the phenyl ring) the contribution to the rotation from this substituent is much changed; the contributions from the other substituents, which in any case are small are changed very little. This offers the possibility for studying the connection between optical activity and the substituent effect in aromatic compounds. Such investigations have been carried out by Betti (114), Rule (115) and Singh *et al.* (116)[1] and their results before 1952 have recently been interpreted in more modern terminology by Nerdel *et al.* (117) who also recently have investigated the connection between optical activity and chemical constitution of the dibenzal compounds of (+)-3-methyl cyclohexanone (118), the benzal compounds of α-phenylethylamine (119) and of substituted hydratropic acids (120). Fredga and Andersson have investigated the isomeric nitro and amino substituted mandelic acids (121, 122, 123).

Pettersson (42) has suggested that the 2-thienyl group is a dominant substituent in those compounds where in the phenyl analog the phenyl group is dominant and that thus the vicinal action of the other substituent is similar on the thiophene analog. This suggestion seems plausible from the similar rotation dispersion in the visible for the phenyl- and thienyl substituted compounds. An investigation of the UV-spectra of thiophenes (11) indicates also that the 235 mμ chromophore in thiophenes is similar in nature to the 250 mμ chromophore in benzenes. Pettersson (42) also pointed out that from the material available it is not possible to decide if the lower rotation of the 2-thienyl analogs depends on shorter wavelength of absorption or on smaller anisotropy of the band. A comparison between the isomeric thiophenes is however easier. As can be seen from Figs. 1–3, where the UV-spectra of the optically active thienylglycolic acids, thienylsuccinic acids and thenylsuccinic acids are given, $\lambda_{max}$ occurs at the same wavelength (235–236 mμ) in all isomers. This makes it probable that the different rotations for 2- and 3-substituted compounds are due to differences in the anisotropy of the 235 mμ band in thiophenes. There might be some connection between the usually greater rotation of 3-substituted compounds and the weaker intensity of their absorption bands, as according to Kuhn (124) weak bands usually have large anisotropy factors.

[1] In this paper reference to earlier works of Singh *et al.* can be found.

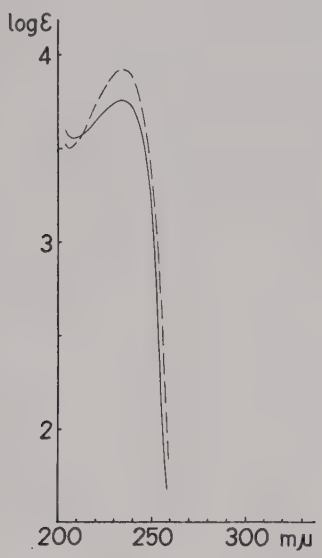



Fig. 1. UV-spectra of – – – – (+)-2-thenyl-succinic acid and —— (+)-3-thenyl-succinic acid.

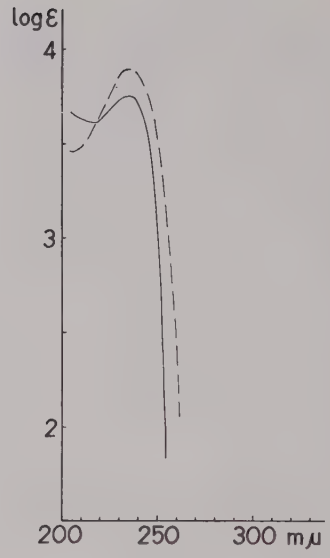



Fig. 2. UV-spectra of – – – – (+)-2-thienyl-succinic acid and —— (+)-3-thienyl-succinic acid.

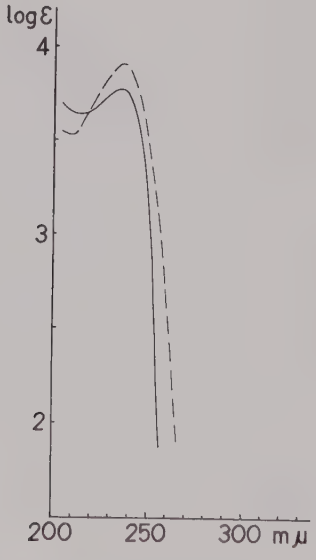



Fig. 3. UV-spectra of – – – – (+)-2-thienyl-glycolic acid and —— (+)-3-thienyl-glycolic acid.

## Side-chain reactivity in thiophenes

From the physical properties investigated from dipole moment measurements (60–62) and dissociation constants (85) it is apparent that the conjugative electron-attracting −M effect[1] increases in the following series, phenyl < 3-thienyl < 2-thienyl, and that also the conjugative electron repelling effect increases in the same order phenyl < 3-thienyl < 2-thienyl. However especially NMR-data indicate that the difference in +M effect between the phenyl and thienyl groups is smaller than the difference in their −M effect. Finally the inductive effect increases in the same series phenyl ≈ 3-thienyl < 2-thienyl. The inductive electron-attracting effect of the 2-thienyl group appears to be much stronger than those of the phenyl and 3-thienyl groups. As mentioned earlier it appears that the −I effects of the phenyl and 3-thienyl groups are of the same magnitude as and opposite in direction to the +M effects, while for the 2-thienyl group −I > +M.

With this knowledge of the electronic properties the following predictions about the influence of the thienyl groups on side-chain reactions are possible. The alkaline hydrolysis of aromatic esters, the nucleophilic substitution of benzyl halide type compounds and prototropic reactions of aryl substituted compounds are chosen as examples of different types of side-chain reactions.

It is well known that the alkaline hydrolysis of esters of benzoic acids is retarded by electron donating substituents in the phenyl ring and facilitated by electron-attracting substituents. Thus a $-OCH_3$ group in the *para* position decreases the rate while a nitro group increases the rate of hydrolysis, relative to the unsubstituted esters (125). If we now turn to the thiophene analogs it is evident that the strong −I effect of the 2-thienyl group, strengthened by the inductomeric effect in the same direction, should facilitate the reaction while the +M effects should retard the reaction. As the combined electron-attracting properties are stronger, ethyl 2-thiophenecarboxylate should be hydrolyzed faster than ethyl benzoate. This is in accordance with the latest kinetic measurements of this reaction (94). For the 3-thienyl group the −I effect is of the same magnitude as for phenyl the +M effect is somewhat stronger. Thus ethyl 3-thiophenecarboxylate should be hydrolyzed slower than ethyl benzoate, which also has been found experimentally (85). The characteristic feature of this and analogous reactions should thus be that the rates are of the same magnitude for benzene and thiophene compounds, a little faster in the 2-substituted thiophenes and a little slower in the 3-substituted ones than in the corresponding benzenes.

It is known that nucleophilic aliphatic substitution in benzylhalides is strongly accelerated by conjugatively electron-donating groups such as methoxyl in the *para* position and strongly retarded by electron-attracting groups like $-NO_2$ in the same position. Okamoto and Brown (126) have recently investigated the solvolysis of substituted phenyl dimethyl carbinyl chlorides and found that the *para* methoxy substituted compound reacted 3360 times faster and the para nitro compound 3900 times slower than the unsubstituted compound. If we now consider a 2-substituted thiophene, its −I effect should retard the reaction and its +M effect (or better expressed, its associated +E-effect) should facilitate the reaction. It is difficult to decide which effect should dominate. The strong effect of the methoxyl group in benzenes suggests however that the electromeric effect is most important, stabilizing the transition state through extended conjugation with the arising empty p orbital.

[1] For the sake of clarity, note that the electronic characteristics are now being considered from the viewpoint of the aromatic nuclei rather than that of the substituents.

For a 3-substituted thiophene the retarding −I effect is much smaller, but the facilitating +E effect is also smaller than in a 2-substituted compound. Stressing again the importance of the conjugative effects in this type of reactions, it seems plausible that the 2-substituted compund is more reactive than the 3-isomer which in turn reacts faster than the benzene analog. There is some evidence in the literature, at least concerning the reactivity of 2-substituted compounds, which shows that they react faster than the phenyl analogs. Cairns and McKusick (127) and Pettersson (128) found that 2-thenyl chloride in the reaction with sodium cyanide in ethanol gave a mixture of ethyl 2-thenyl ether (25 % yield) and 2-thenyl cyanide (32 % yield) while benzyl chloride under the same conditions gave a high yield of benzyl cyanide uncontaminated with ethyl benzyl ether. Cairns and McKusick (127) also found by allowing benzyl chloride and 2-thenyl chloride to compete for a deficit of sodium amoxide in amyl alcohol that 2-thenyl chloride reacted about three times faster than benzyl chloride.

For the third type of reaction chosen, the effect of the thienyl groups is easily understandable. In prototropic reactions (129) such as the bromination or deuteration of benzylketones or derivatives of phenylacetic acid, or the base catalyzed racemization of the corresponding optically active compounds, the rate-determining step is often the dissociation of a proton from the $\alpha$-carbon. The effect of substituents in the phenyl group is thus the reverse of the case just discussed. Electron-attracting substituents thus facilitate the ionization of the proton. In this type of reactions, the strong −I effect and −E effect of the 2-thienyl group are in the same direction and the 2-thienyl isomer should undergo such reactions appreciably faster than the phenyl analog. In the 3-isomer, the −I effect is of the same order as in the benzene compound, but its stronger −E effect should render it somewhat more reactive than the benzene compound.

This is in accordance with qualitative observations by Pettersson (106) and by the present author (14) on the base-catalyzed racemization of the isomeric thienylsuccinic acids. Under conditions where phenylsuccinic acid is not racemized at all, partial racemization of 3-thienylsuccinic acid and complete racemization of 2-thienylsuccinic acid is obtained.

In a quantitative study of the base-catalyzed racemization of the phenyl and thienyl substituted glycolic acids at 90°, the present author (17) found that 2-thienylglycolic acid is racemized 33 times faster than mandelic acid and 20 times faster than 3-thienylglycolic acid, in agreement with the predictions made.

## Metalation of 3-substituted thiophenes

With the now easy availability of 3-substituted thiophenes and with an increased knowledge of the effect of substituents in position 3, it was of interest to study the effect of substituents on reactions of thiophene. The metalation with *n*-butyllithium has been chosen, as this reaction clearly illustrates differences between thiophene and benzene.

Benzene is metalated extremely slowly and to a very small extent by *n*-butyllithium in ether (130). Most benzene derivatives containing substituents with unshared electron pairs also undergo metalation sluggishly (131). Reaction times of 40–60 hours are normal and the yields are low. Thiophene on the contrary is metalated rapidly and almost quantitatively by *n*-butyllithium in ether (132). Through a study of the

directing effect of substituents in position 3, valuable information about the mechanism of this reaction should be obtained. If the yields are as high as in the metalation of thiophene itself, the reaction is of great preparative importance, not only for the synthesis of otherwise difficultly available thiophene derivatives, but also for the preparation of aliphatic compounds through Raney-nickel desulphurization.

A discussion of the two different interpretations of the mechanism of the metalation has recently been given by Gilman and Morton (133). According to Roberts and Curtin (134) and Sunthankar and Gilman (135) the rate determining step is a nucleophilic attack of the anion on hydrogen. For this type of reaction, Bryce-Smith (136) has introduced the term protophilic. According to these authors the most positively polarized, most acidic hydrogen is attacked by the anion. Morton (137), on the other hand, has suggested that metalation belongs to electrophilic aromatic substitution with $Li^+$ as the electrophilic reagent. The present author (7) has suggested that the primary step in the metalation of thiophene is the coordination of the metalating agent to the sulphur followed by an attack by the anion on the most acidic hydrogen. It has also been suggested (6) that this coordination to the sulphur is stronger than to a $-OCH_3$ group, as Sicé (76) exclusively obtained metalation in position 5 in the metalation of 2-methoxythiophene. The suggestion by Sicé that this should depend upon the radicaloid nature of metalation and that radicaloid reagents contrary to electrophilic ones always prefer the $\alpha$-positions of thiophene seems somewhat unlikely.

The metalation of 3-methylthiophene (7), 3-phenylthiophene (55), 3-methoxythiophene (6), methyl 3-thienyl sulphide (9) and methyl 3-thienyl sulphone (9) has been investigated. In connection with the synthesis of 3-thienyllithium, metalation of 3-bromothiophene (7) was obtained under certain circumstances. The metalated compounds were isolated in the customary manner as the carboxylic acids through reaction with carbon dioxide. The reactions were in all cases very rapid and the yields high, so that the expectations of the preparative usefulness of this method have been fulfilled.

3-Methylthiophene is metalated in position 5, which, as the present author (7) has pointed out, gives strong support for the protophilic mechanism. Electrophilic aromatic substitution occurs as has been mentioned earlier almost exclusively in position 2 (77).

The inductive effect of the phenyl group is contrary to that of the methyl group and metalation should thus be expected to occur in position 2. It has however been found (55) that a mixture of mainly 3-phenyl-5-thiophenecarboxylic acid and 3-phenyl-2-thiophenecarboxylic acid was obtained on carbonation, which could not be separated through fractional crystallization. It could however be proved that the main product was 3-phenyl-5-thiophenecarboxylic acid as upon desulphurization 4-phenylvaleric acid was obtained as the main product. These results may indicate that the metalation with *n*-butyllithium is sensitive for steric effects. Steric effects have also been supposed by Gilman and Spatz (138) to be responsible for the *meta* metalation of triphenylamine.

Especially interesting is the effect of $-I+M$ substituents such as $-OCH_3$, $-SCH_3$ and –Br. The information obtained through NMR shows that at least the methoxyl group has a permanent conjugative effect in the ground state, which tends the make hydrogen 2 less acidic than hydrogen 5. In spite of this, 3-methoxythiophene (6) as well as methyl 3-thienyl sulphide (9) are metalated in position 2. As there is no reason to suppose that the mechanism for the metalation of this compounds is different from that for 3-methylthiophene, the most probable explanation is that the inductive elec-

tron-attracting effect of the substituents which during the reaction also is strenghtened by the inductomeric effect in the same direction, determines the place of substitution. The great importance of the inductive effect in the metalation of benzene derivatives has been pointed out by Wittig (139), although it should be remembered that in the metalation of benzene derivatives, coordination occurs at the substituent which suppresses its conjugative effect besides making it *ortho* directing.

Metalation of methyl 3-thienyl sulphone (9) occurred in the side-chain, showing that the activating effect of the sulphone group is stronger than that of the aromatic sulphur.

In an investigation by the present author and Halvarsson (18) on the isotope effect in the metalation of thiophene containing tracer amounts of 2-tritiumthiophene, it has been found that protium reacts at least six times faster than tritium in the metalation with *n*-butyllithium, showing that the mechanism is different from bromination and nitration of benzene (140) where no isotope effect has been obtained. The large isotope effect is in accordance with protophilic activity of organolithium compounds and shows that the elimination of the hydrogen is the rate-determining step.

## Determination of structure of thiophenes

In connection with the experiments on metalation, the problem of the determination of the structure of the products arose. Reliable methods have also become important for structure determination of naturally occurring thiophenes. Wheland (141) has pointed out that the classic method of isomer number is not even theoretically possible in the thiophene series.

The present author has shown that different physical methods can be used with great certainty for the identification of thiophenes. The 13 $\mu$ band in the IR-spectrum can be used to distinguish 3-substituted thiophenes from the 2-isomers (3, 6, 9, 12). It might also be possible, when enough experimental material is available, to use the C–H bending region for the identification of disubstituted thiophenes as in the benzene series (142). There are also characteristic differences in the UV-spectra (11) which can be used for identification.

The best method for identification is provided by the NMR-spectra. It is of course very easy with such spectra to distinguish a symmetrical substituted compound as 2,5-dinitrothiophene from an unsymmetrical as 2,4-dinitrothiophene as in the first mentioned case only one sharp resonance is obtained. It has however been found (9, 12) that the spin-spin coupling constants between the different remaining aromatic hydrogens in the thiophene nucleus can be used for identification of disubstituted thiophenes. The J values obtained obtained are $J_{23} - 5.4 \pm 0.6$ c/s; $J_{34} = 3.8 \pm 0.3$ c/s; $J_{25} = 2.7 \pm 0.4$ c/s; $J_{35} = 1.6 \pm 0.3$ c/s. The coupling constants are thus well separated, making identification easy. The variation in a disubstituted series appears from the compounds hitherto recorded, to be about 10 %. The spin-spin coupling constants have been used for the determination of the structure of the product obtained on metalation of methyl 3-thienyl sulphide (9).

Raney-nickel desulphurization has also been used for structure determination (6) and conditions worked out for avoiding the elimination of certain substituents (16). Finally, also cyclization reactions have been used (6) in order to establish structure.

## SUMMARY

New methods for the preparation of 3-substituted thiophenes have been worked out. In 3-thienyllithium a very useful intermediate for the preparation of this type of compounds has been found.

IR-spectra, UV-spectra and NMR-spectra of 3-substituted thiophenes have been studied and compared with the corresponding 2-isomers and phenyl analogs. Valuable information about the structural differences in these compounds was obtained, which made it possible to discuss the difference in the effect of substituents in position 2 and position 3 in thiophene on aromatic substitution reactions. An explanation on the special effect of substituents in position 3 on the reactivity in position 4 has been given.

The influence of the isomeric thienyl groups on side-chain reactivity has also been discussed and compared with the benzene analogs. The base-catalyzed racemization of mandelic acid and the thienylglycolic acids has been investigated as an example of such a type of reaction.

The optical activity of 3-substituted thiophenes has been studied and compared with the corresponding 2-isomers and phenyl analogs. The results obtained indicate that in most cases the rotations are larger for the 3-isomers than the 2-isomers. The differences in rotation values seem mainly to depend upon differences in the anisotropy of the 235 m$\mu$ band in the thiophenes. The quasi-racemate method has been used for the determination of the configuration of optically active 3-substituted thiophenes. A new determination of the configuration of mandelic acid has been achieved.

The effect of substituents in position 3 on the metalation with *n*-butyllithium has been investigated, and information about the mechanism of this reaction has been obtained. This reaction is very usuful for the preparation of various substituted thiophenes.

The use of UV-spectra, IR-spectra and especially NMR-spectra for the determination of the constitution of substituted thiophenes has been discussed. Chemical methods such as Raney-nickel desulphurization and ring-closure reactions have also been used for such determinations.



## ACKNOWLEDGEMENTS

The present paper is a review on investigations on 3-substituted thiophenes carried out during 1953–1958. The literature up to August 1958 is discussed. This work has been carried out at the Institute of Chemistry, University of Uppsala (1953–1955) and continued and finished at the Institute of Organic Chemistry, Royal Agricultural College, Uppsala (1956–1958).

To my teacher in Organic Chemistry, Professor Arne Fredga, I wish to express my sincere gratitude for his kind interest in my work and for many stimulating discussions. His profound knowledge of thiophene chemistry and optical activity has been a great help. I am very much indebted to the Head of this Institute, Professor Nils Hellström, for his kind interest and for all facilities put at my disposal.

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*Institute of Organic Chemistry, Royal Agricultural College, Uppsala, August 1958.*

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